DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 1/22/2010, are acknowledged and entered. Claims 6-7 have been cancelled by Applicant. Claims 1-5, 8-16, and 18 are presented for examination.

Claims 1-3, 8-12, 15-16, and 18 remain withdrawn from consideration as being drawn to a non-elected invention/species.

Claims 4-5 and 13-14 are presently under examination and are the subject of this Office Action.

Response to Arguments

Any previous rejections and/or objections to claims 6-7 are **withdrawn** as being moot in light of Applicant's cancellation of the claims.

Applicants' arguments, filed 1/22/2010, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112 – 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 4-7 and 13-14 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is **withdrawn** in light of Applicant's amendments.

Claim Rejections - 35 USC § 112 – 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4-5 and 13-14 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to compounds of Formula (I) as disclosed in the specification at pages 3-6 and 8-18 and recited in instant claims 4-5 and 13-14. Applicants disclose that the compounds of Formula (I) disclosed in the specification and recited in the instant claims are useful in the treatment of proliferative disease (page 1) such as proliferative diseases depending on topoisomerase II (page 8). Disclosed diseases intended to be treated with the disclosed compounds include hyperproliferative conditions such as leukemias, hyperplasias, fibrosis (especially pulmonary, but also other types of fibrosis, such as renal fibrosis), angiogenesis, psoriasis, atherosclerosis and smooth muscle proliferation in the blood vessels, such as stenosis or restenosis following angioplasty. Proliferative diseases also include tumors with low levels of topoisomerase II activity. Preferred diseases include benign or especially malignant tumor, more preferably carcinoma of the brain, kidney, liver, adrenal gland, bladder, breast, stomach (especially gastric tumors), ovaries, colon, rectum, prostate, pancreas, lung (especially SCLC), vagina, thyroid, sarcoma, glioblastomas, multiple myeloma or gastrointestinal cancer, especially colon carcinoma or colorectal adenoma, or a tumor of the neck and head, an epidermal hyperproliferation, especially psoriasis, prostate hyperplasia, a neoplasia, especially of epithelial character, preferably mammary carcinoma, or a

leukemia. Most preferred are breast tumors with over-expressed ErbB-2 and low topoisomerase II levels (page 19).

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

That factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain). As illustrative of the state of the art, the examiner cites Sausville *et al.* (Cancer Research, 2006, vol. 66, pages 3351-3354) and Johnson *et al.* (British J. of Cancer, 2001, 84(10):1424-1431).

Sausville *et al.*, cited for evidentiary purposes, teaches that traditionally explored tumor model systems are insufficient to predict how actual human beings will respond to treatment in the clinic (page 3351, left column). Even when drugs with evidence of anticancer activity in preclinical *in vivo* models are given their maximum tolerated dose in humans, they frequently fail to produce useful activity in humans (*id.*). Also, with regard to unpredictability, Johnson *et al.*, also cited for evidentiary purposes, teach that the *in vivo* activity of 39 different agents in a particular histology in a tumor model did not correlate to activity in the same human cancer. *In re Fisher*, 427 F.2d 833, 166

USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Further, the mode of action of anticancer agents is often unknown or very unpredictable and administration of such agents is often accompanied by undesirable side effects.

These articles plainly demonstrate that the art of treating cancer, particularly in humans, is extremely unpredictable, particularly in the case of a single compound or genus of compounds being used to treat any and all cancers.

2. The breadth of the claims

The claims are extremely broad insofar as they are drawn to a plethora of compounds of Formula (I) having a multitude of possible substituents at the R_2, R_6, and R_8 positions.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no working examples demonstrating that any compound of Formula (I) has *in vivo* therapeutic activity against any proliferative disease.

The specification provides an *in vitro* ATPase assay to monitor ATP hydrolysis to determine the inhibition potential of the disclosed compounds on TOPO II ATPase activity (pages 20-21).

The specification provides an *in vitro* human topoisomerase II at page 21.

Table 6 of the specification discloses 74 examples of compounds of Formula (I) and provides their topoisomerase II inhibition data. The percent inhibition values given in the Table are after incubation with 10 μM of a compound of the invention. According to the legend on page 52, a "-" indicates that the given compound results in less than 50% at 10 μM. Over half of the tested compounds (44/74) resulted in less than 50% inhibition of topoisomerase II *in vitro* at a dose of 10 μM.

The specification provides only very general guidance with regard to doses and administration regimens necessary to treat all of the various proliferative diseases

claimed, particularly in humans. In this regard, Applicants disclose that the dose of a compound of Formula (I) will be 3 mg to 10 g for human patients (page 28).

There is no working example of treatment of any proliferative disease in cells, animals or man. The topoisomerase II assay provides evidence that some (less than 50%) of the present compounds of Formula (I) inhibit topoisomerase II more than 50% at a dose of 10 μM *in vitro*. However, inhibition of a receptor does not predictably correlate to clinical efficacy. Thus, there are no working examples correlating inhibition of topoisomerase II with efficacy in the treatment of a proliferative disease using the claimed compounds (*i.e.,* Applicants have not shown that inhibition of topoisomerase II with a compound of the invention correlates to *in vitro* and/or *in vivo* efficacy against a proliferative disease with the same compound).

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed genus of compounds could be predictably used as a treatment for cancerous cell growth as inferred in the claims and contemplated by the specification.

Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

In the instant case, Applicants have presented a general idea that because some of the instantly claimed compounds of Formula (I) inhibit topoisomerase II *in vitro* then the broad scope of compounds of Formula (I) must therefore, *a priori*, be useful in the treatment of proliferative diseases. However, the claims encompass a multitude of compounds (perhaps millions) having a plethora of chemically and biologically distinct substituents. Applicants tested 74 compounds having a limited number of substituents at the R_2, R_6, and R_8 positions (see Table 6). For example, 29 of the 74 compounds had a

benzothiazol-6-yl group in the R_2 position; 37 of the 74 compounds had a **t-butyl** group in the R_6 position; and 47 of the 74 compounds had a **hydrogen** at the R_8 position.

It is evident that a very small percentage of the claimed compounds were actually synthesized and tested (for inhibition of topoisomerase II *in vitro*) by Applicants and all of the synthesized compounds were closely related in structure having a limited number of distinct substituents compared to the broad scope of possible substituents encompassed by the claimed compounds of Formula (I). Thus, the compounds actually synthesized and screened by Applicants do not correlate in scope with the claimed subject matter. Given the extremely diverse compounds encompassed by the claims and the limited examples provided in the specification, the skilled artisan cannot predict what structural features (other than those of the compounds actually synthesized and tested) are important for inhibition of topoisomerase II. This is especially true when one considers that over half of the tested compounds (44/74) resulted in less than 50% inhibition of topoisomerase II *in vitro* at a dose of 10 μM.. In other words, the structure activity relationship demonstrated in the examples is limited to a very small sub-genus of compounds.

Determining if any particular claimed compound would treat any particular proliferative disease state would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it to clinical trials or to testing in an assay known to correlate to clinical efficacy of such treatment. This is undue experimentation given the limited guidance and direction provided by Applicants. As noted *supra*, even *in vitro* and *in vivo* assays do not always correlate to efficacy in humans and are not generally predictive of clinical efficacy.

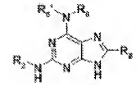
Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since enable a patentable use of the claimed compounds of Formula (I) a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Response to Arguments

Applicants traverse the instant rejection, stating that they have amended claim 4 to limit R2 to naphthalynyl and benzothiazolyl, i.e., "more narrowly tailored to cover specific examples shown in the specification". Applicants further argue that one of skill in the art could make the current claim scope without undue experimentation.

Applicant's arguments filed 1/22/2010 have been fully considered but they are not persuasive. Applicant's claimed compounds are purported to be inhibitors of topoisomerase and therefore useful in treating "proliferative diseases" in patients (page 1) such as proliferative diseases depending on topoisomerase II (page 8). Disclosed diseases intended to be treated with the disclosed compounds include hyperproliferative conditions such as leukemias, hyperplasias, fibrosis (especially pulmonary, but also other types of fibrosis, such as renal fibrosis), angiogenesis, psoriasis, atherosclerosis and smooth muscle proliferation in the blood vessels, such as stenosis or restenosis following angioplasty. Proliferative diseases also include tumors with low levels of topoisomerase II activity. Preferred diseases include benign or especially malignant tumor, more preferably carcinoma of the brain, kidney, liver, adrenal gland, bladder, breast, stomach (especially gastric tumors), ovaries, colon, rectum, prostate, pancreas, lung (especially SCLC), vagina, thyroid, sarcoma, glioblastomas, multiple myeloma or gastrointestinal cancer, especially colon carcinoma or colorectal adenoma, or a tumor of the neck and head, an epidermal hyperproliferation, especially psoriasis, prostate hyperplasia, a neoplasia, especially of epithelial character, preferably mammary carcinoma, or a leukemia. Most preferred are breast tumors with over-expressed ErbB-2 and low topoisomerase II levels (page 19).

Applicants disclose a genus of compounds of Formula (I) suitable for use in the methods disclosed in the instant specification and recited in claim 1.

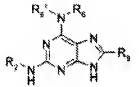


(I)

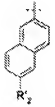
wherein:

R_2 is substituted or unsubstituted lower alkyl, substituted or unsubstituted aryl, substituted or unsubstituted bicyclic aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted bicyclic heteroaryl;

Claim 4 has been amended to recite compounds of Formula (I):



wherein R2 is selected from



and

where R'2 is H or a solubilizing group of the Formula:

–X-Y-A

where X is O, S, -$(CH_2)_n$-, NH or N(lower alkyl);

Y is -$(CH_2)_n$-;

n is 1-4; and

A is $NR_{10}R_{11}$ where R_{10} and R_{11} are independently H or C_1-C_3 lower alkyl, or R_{10} and R_{11} with the nitrogen atom form a 3- to 8-membered heterocyclic ring containing 1-4 nitrogen, oxygen or sulfur atoms, or A is

where X is as defined above.

R'6 is H or lower alkyl;

R8 is lower alkyl or C3-C5 cycloalkyl; and

R6 is substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted bicyclic aryl, substituted or unsubstituted bicyclic heteroaryl, or a substituted or unsubstituted aliphatic residue; or R8 and R'6 with the N atom form a substituted or unsubstituted heterocyclic radical; or pharmaceutically acceptable salts thereof.

Topoisomerase II inhibition (in vitro) by compounds of the invention was evaluated by Applicants (Table 6). Of the 74 compounds tested, 29 of the compounds contained the benzothiazol-6-yl substituent at the R2 position and 9 of the compounds contained the naphthalen-2-yl substituent at the R2 position. Of the 29 benzothiazol-6-yl substituted compounds, 17 of the compounds (59%) elicited less than 50% inhibition of topoisomerase II at 10 μM compound concentration. Likewise, of the 9 naphthalen-2-yl substituted compounds, 5 of the compounds (56%) elicited less than 50% inhibition of topoisomerase II at 10 μM compound concentration.

The skilled artisan, presented with Applicants' claimed compounds of Formula (I) and data presented in Table 6 would not have imbued with a reasonable expectation that such compounds could be predictably used to inhibit topoisomerase II and treat proliferative diseases as disclosed in the instant specification. It is readily apparent from Applicants' in vitro data that structural differences have a significant, unpredictable impact on inhibition of topoisomerase II.

For example, a compound of Formula (I) wherein R2 is benzothiazol-6-yl, R6 is tert-butyl, and R8 is ethyl inhibited greater than 80% topoisomerase II at a concentration of 10 μM. However, by merely changing the R8 substituent to another "lower alkyl" or "C3-C5 cycloalkyl" (e.g., propyl, isopropyl, cyclopentyl), topoisomerase inhibition was significantly reduced to less than 50% (compare Examples 27, 32, 33, and 34 in Table 6). Further evidence of the unpredictability of using compounds of Formula I to inhibit topoisomerase II and treat proliferative diseases is demonstrated by the fact that a compound of Formula (I) wherein R2 is naphthalen-2-yl, R6 is tert-butyl, and R8 is ethyl (Example 73), demonstrated less than 50% inhibition of topoisomerase II, despite the fact that this compound merely substitutes naphthalen-2-yl for benzothiazol-6-yl. As noted

above, the compound of Formula (I) wherein R2 is benzothiazol-6-yl, R6 is tert-butyl, and R8 is ethyl inhibited greater than 80% topoisomerase II.

It is readily apparent from Applicants' data that they have discovered a small sub-genus of compounds capable of inhibiting topoisomerase II. The structure-activity relationships demonstrated in Table 6 clearly show that minor changes in "active" compounds significantly and unpredictably lower the activity of the compounds. As discussed supra, *Genentech Inc. vs. Nova Nordisk* states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997). In the instant case, Applicants have provided the skilled artisan with perhaps 23 compounds encompassed by the instant claims that inhibit topoisomerase II. However, structurally related compounds also encompassed by the claims, often differing in only one carbon atom (*e.g.*, ethyl vs. propyl), are not effective inhibitors of topoisomerase II. The skilled artisan cannot predict what structural features are required for inhibition of topoisomerase II based on Applicants' disclosure and in vitro topoisomerase II inhibition data.

Accordingly, the Applicants have failed to provide enabling disclosure for use of the claimed genus of compounds of Formula (I).

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the

advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Primary Examiner, Art Unit 1614

April 7, 2010